UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR		ATTORNEY DOCKET NO.
09/035,596	03/05/98	GUNZBURG	W	GSF98-01

021005 HM22/1121
HAMILTON BROOK SMITH AND REYNOLDS, P.C.
TWO MILITIA DR
LEXINGTON MA 02421-4799

EXAMINER	
CHEN, S	
ART UNIT	**PAPER NUMBER**
1633	14

DATE MAILED: 11/21/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/035,596	Gunzburg et al.
Examiner	**Group Art Unit**
Shin-Lin Chen	1633

☒ Responsive to communication(s) filed on *Sep 6, 2000*

☐ This action is FINAL.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1, 2, 4, 5, 9-14, 16-19, 23-33, and 36-94* is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1, 2, 4, 5, 9-14, 16-19, 23-33, and 36-94* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *13*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

— SEE OFFICE ACTION ON THE FOLLOWING PAGES —

DETAILED ACTION

The amendment filed 9-6-00 has been entered. Claim 46 has been canceled. Claims 1, 5, 18, 26, 27, 30, 31, 37, 39, 40, 41, 44, 45, 53, 55, 56 and 70 have been amended. Claims 74-94 have been added. Claims 1, 2, 4, 5, 9-14, 16-19, 23-33 and 36-94 are pending.

Information Disclosure Statement

Applicant is requested to point out the subject matter of the co-pending applications cited on page 2 of the transmitter letter of the supplemental information disclosure statement filed 9-6-00 that is closely related to the present application, hence said co-pending applications could be considered by the examiner.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 4, 5, 9, 14, 29, 30, 36, 44, 45, 47-50, 55-57, 62, 76 and 84 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "U3 region of MMTV" in claims 4, 9, 14, 29, 36, 57, 62, 76 and 84 is vague and render the claims indefinite. It is unclear what the nucleotide sequence is for the U3 region

of MMTV. The specification of the present application fails to define the term "U3 region of MMTV".

The term "0.6 Kb PstI murine MMTV promoter fragment" in claims 5 and 30 is vague and renders the claims indefinite. It is unclear what the nucleotide sequence is for the 0.6 Kb PstI region of murine MMTV. The specification of the present application fails to define the term "0.6 Kb PstI murine MMTV promoter fragment".

The term "proximal 445 bp of the murine WAP promoter" in claims 44 and 55 is vague and renders the claims indefinite. Murine WAP promoter encompasses promoter sequences derived from various murine species. It is unclear what 445 bp of which WAP promoter is intended.

The term " 320 bp XhoI/XbaI fragment of the murine WAP promoter" in claims 45 and 56 is vague and renders the claims indefinite. Murine WAP promoter encompasses promoter sequences derived from various murine species. It is unclear what 320 bp XhoI/XbaI fragment of which WAP promoter is intended, because not every WAP promoter has XhoI/XbaI restriction sites.

Claims 47-50 are indefinite because it depends on canceled claim 46.

The term "rodent MMTV" in claims 74-81, 91 and 92 is vague and render the claims indefinite. The term "MMTV" is an abbreviation of "**mouse** mammary tumor virus". It is unclear whether there is other "**mouse** mammary tumor virus" derived from species other than **mouse**.

3. Claims 37-40, 70-73, 92 and 94 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: whether, sufficient therapeutic gene product is expressed for a sufficient duration of time and whether the expressed therapeutic gene has any therapeutic effect on the targeted cells.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1, 2, 4, 5, 9-14, 16-19, 23-33 and 36-94 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for construction of vectors pMMTV-BAG and pWAP-BAG containing β-galactosidase gene under the control of MMTV and WAP, respectively, and the expression of β-galactosidase in explanted normal primary human mammary tissue infected with virus containing said vectors set forth above, does not reasonably provide enablement for any retroviral vector comprising any therapeutic gene under the control of a MMTV promoter or a WAP promoter and said therapeutic gene is expressed in a cell *in vivo,* a method of expressing said therapeutic gene in a human cell *in vivo*, any pharmaceutical composition comprising a DNA construct comprising any therapeutic gene under the control of a MMTV promoter or a WAP promoter, and a method for the treatment of human mammary

carcinoma comprising administering to a human a retroviral particle expressing any therapeutic gene under the control of a MMTV or WAP promoter *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. .

The claims are drawn to a retroviral vector comprising a therapeutic gene under the control of a MMTV promoter or a WAP promoter and said therapeutic gene is expressed in a cell, such as a human cell, a method of expressing said therapeutic gene in a human cell, a pharmaceutical composition comprising a DNA construct comprising said therapeutic gene under the control of a MMTV promoter or a WAP promoter, and a method for the treatment of human mammary carcinoma comprising administering to a human a retroviral particle expressing said therapeutic gene under the control of a MMTV or WAP promoter.

The claims are also drawn to a retroviral vector comprising a heterologous gene under the control of a MMTV promoter or a WAP promoter and said heterologous gene is expressed in a cell, such as a human cell, a method of expressing said heterologous gene in a human cell, a recombinant retroviral particle or provirus comprising said retroviral vector or a DNA construct containing a heterologous gene under the control of a MMTV promoter or WAP promoter, a packaging cell line harboring said retroviral vector, and isolated human cell comprising said retroviral vector, and a capsule encapsulating said packaging cell line.

The claims read on expression of a therapeutic gene *in vitro* or *in vivo*. The claims also read on the use of the retroviral vector, the retroviral particle or provirus containing said

retroviral vector or the DNA construct set forth above, the packaging cell line comprising said retroviral vector, the human cell containing said retroviral vector and encapsulated cells containing said packaging cell line for gene therapy *in vitro* or *in vivo* in light of the specification.

The specification of the instant invention discloses the construction of vectors pMMTV-BAG and pWAP-BAG containing β-galactosidase gene under the control of MMTV and WAP, respectively. The specification shows the expression of β-galactosidase in explanted normal primary human mammary tissue infected with virus containing said vectors set forth above.

A pharmaceutical composition is a composition which implies *in vivo* applicability such that therapeutic effects against a particular disease or a disorder are obtained. It is well known in the art that β-galactosidase is a molecular marker and not a therapeutic gene, and such is generally not considered to be indicative of therapeutic gene expression. The expression of a β-galactosidase in explanted normal primary human mammary tissue infected with vectors pMMTV-BAG and pWAP-BAG is not considered to enable therapeutic gene expression under the control of a MMTV promoter or a WAP promoter, since expression of a marker gene does not correlate with expression of a gene *in vivo*, such that the expression provides for a therapy. It is unclear that expression of a marker gene relates in any way to successful expression of other genes such that a therapy would be obtained.

The specification fails to provide adequate guidance and evidence that administration of a vector expressing a β-gal or any therapeutic gene product *in vitro* or *in vivo* would provide

sufficient expression of said β-gal or said therapeutic gene product for a duration of sufficient time to effect therapeutic effects for a particular disease or disorder, such as disorders or diseases of human mammary cells *in vitro* or *in vivo*. The specification fails to provide adequate guidance and evidence for the sufficient expression of any heterologous gene or any therapeutic gene under the control of any MMTV promoter or any WAP promoter in the retroviral vector or other vector for sufficient time *in vivo* such that therapeutic effects are provided for a particular disease or disorder, or for using said retroviral vector expressing any heterologous gene or therapeutic gene for the treatment of disorders or diseases of human mammary cells *in vitro* or *in vivo*.

The nature of the invention being gene therapy, the state of the prior art was not well developed and is highly unpredictable. Verma et al., 1997 (V3) states that out of the more than 200 clinical trials currently underway, no single outcome can be pointed to as a success story (see Verma et al., page 239, col. 1). For instance, numerous factors complicate the gene therapy art which have not been shown to be overcome by routine experimentation. Eck et al., 1996 (W3) reports that the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced are all important factors for a successful gene therapy *in vivo*. These factors differ dramatically based

on the vector used, the protein being produced, and the disease being treated (e,g, bridging pages 81-82). Verma states that one major obstacle to success has been the inability to deliver genes efficiently and obtain sustained expression (see Verma et al., page 239, col. 3). The instant specification does not provide any *in vitro* or *in vivo* working examples for gene therapy. The specification only shows the expression of β-galactosidase in explanted normal primary human mammary tissue infected with retrovirus containing the vectors set forth above but fails to teach how to construct any therapeutic vector other than retroviral vector, how to deliver it such that it reaches targeted cells, or that any therapeutic level of expression could be achieved to effect a therapeutic response to any particular disease.

Furthermore, the vectors for gene transfer encounter various problems with gene transfer efficiency. Orkin et al. 1995 (X) reported that none of the available vector systems for gene transfer is entirely satisfactory, and many of the perceived advantages of vector systems have not been experimentally validated. Retroviruses infect and integrate only dividing cells. Other problems associated with retroviruses include cumbersome preparation and relatively low titer, size constraints on inserted genes, and the potential for genetic damage due to random integration in the host genome. Adenovirus, Herpesvirus and poxvirus all have the problem of relatively high immunogenicity and complexity of its genome. Adeno-associated virus requires replicating adenovirus to grow and no helper cell line available. Direct administration of DNA or DNA complexes (e.g., liposomes) has disadvantages of lower efficiency of gene transfer (compared with viruses) and the absence of mechanisms for specifically maintaining the introduced DNA

within the cell. In terms of the small scale clinical experiment which is referred to as "clinical trials", the efficacy has not been established for any gene therapy protocol, adverse short term effects related to gene transfer protocols appears to vary, depending on the nature of the virus used as a vector and the patient to which it is administered. Because clinical success is still so limited, it is not possible to exclude longterm adverse effects of gene transfer therapy, the multiple integration events resulting from repeated administration of large doses of retroviruses theoretically pose a risk for leukemic transformation. It is not always possible to extrapolate results from experiments in non-human animals to human studies.

Shao et al. shows that encapsulated cells may be used for prolong delivery of a granulocyte-macrophage colony stimulating factor (GM-CSF) to a tumor site. However, Aebischer et al. reports various problems of encapsulated cells for the treatment of disorder or diseases. Aebischer et al., 1991 (U3) encapsulated PC12 cells in polyelectrolyte-based microcapsules or thermoplastic-based macrocapsules and maintain *in vitro* or transplanted in a rat experimental Parkinson model for 4 weeks. They point out that unencapsulated PC12 cells can lead to the formation of lethal tumors in rats, and do not survive if transplanted into the nervous system of either guinea pigs or mice. The presence of a hydrogel within the microcapsule core possibly impeded cell movement within the capsule, resulting in densely-packed cell aggregates and because their poor mechanical properties, microcapsules are more difficult to implant. Often the implanted microcapsules lost their spherical shape and the retrieval of microcapsules is not possible without significant injury to the brain. In addition,

alginate-like materials is found in the vicinity of some microcapsules rasing questions about the stability of the microcapsules *in vivo*. It is also unclear that if the encapsulated cells will grow within the microcapsule, although the encapsulated cells does not trigger immune response from the host as shown by Aebischer et al. If the cells continue to grow within the microcapsule, it is possible the cells could burst out of microcapsule and trigger immune response. Because the claimed invention encompasses any type of cells containing therapeutic gene under the control of a WAP promoter for the treatment of disease of human mammary cells, administration of cells into immunologically incompatible host, between different species or different individuals in same species for example, would stimulate immune response from the host. Therefore, it is considered to be unpredictable to expect to any degree whether cells or encapsulated cells containing any therapeutic gene would exhibit any therapeutic effect on treating disease of human mammary cells. The specification as filed fails to provide any particular guidance for such.

In view of the lack of guidance in the specification on how to treat a particular disease or disorder or disorders or diseases of human mammary cells with encapsulated cells containing a construct comprising a heterologous gene or a therapeutic gene under the control of a MMTV promoter or a WAP promoter and the human unpredictability in art, it would have required undue experimentation for one skilled in the art at the time of the invention to practice over the full scope of the invention claimed. This is particularly true given the nature of the invention, the state of the prior art, the breadth of the claims, the amount of experimentation necessary, the

absence of working examples and scarcity of guidance in the specification, and the unpredictable nature of the art.

The quantity of experimentation required to practice the invention as claimed would include isolation of any therapeutic gene which is yet to be identified, determination of the function of said therapeutic gene, generation of a DNA construct or a recombinant retroviral vector comprising a heterologous gene or a therapeutic gene under transcriptional control of a MMTV or a WAP regulatory sequence, generation of a retroviral particle or cells containing said DNA construct or retroviral vector, generation of encapsulated cells comprising a core containing said cells, determination of therapeutic effects of the DNA construct, retroviral vector and encapsulated cells on treating any disease or disorder, or disorders or diseases of human mammary cells including human mammary carcinoma *in vivo*.

The specification also fails to provide adequate guidance and demonstration as to whether any WAP promoter derived from any organism other than mouse can direct gene expression in human mammary cells or any other human cells, and whether a MMTV promoter can direct gene expression in any human cell type other than human mammary gland cells or human bladder carcinoma cells. The specification indicates that "One regulatory element demonstrated to give rise to expression in the pregnant and lactating mouse mammary gland is a small region of the rodent WAP promoter. It is therefore not predictable that this regulatory element will function at all to direct expression in human mammary cells and/or allow expression in human mammary

carcinoma cells" (specification, page 2, lines 15-25). The mechanisms of stimulating downstream gene expression of various WAP promoters derived from different organisms may vary because the difference of the core elements of WAP promoters and the cellular interacting transcriptional factors in the cells may vary from species to species. Therefore, it would have been unpredictable whether any WAP promoter other than the mouse WAP promoter will direct gene expression in human mammary cells or any other human cells.

Different cell types may have different mechanisms in the transcriptional control of gene expression and the transcriptional machinery in different cell type could differ. Thus, gene expression via a MMTV promoter in normal human mammary gland cells or human bladder carcinoma cells does not necessarily imply that the MMTV promoter can direct gene expression in other human cell types. Further, the MMTV promoter is known in the art to be a mammary cell-specific promoter, it is likely that the MMTV promoter can not direct gene expression in any human cell type other than mammary cells.

Petitclerc et al., 1995 (V4) teaches that rabbit WAP promoter and MMTV LTR are highly efficient in directing gene expression *in vitro* in various cell lines but they are only moderate efficient in transgenic mice (e.g. abstract). Petitclerc points out that "the efficiency of transgene is in most cases largely unpredictable" (e.g. introduction). Thus, although the MMTV promoter or Wap promoter could direct gene expression *in vitro*, it would be unclear whether both MMTV promoter and WAP promoter could direct gene expression *in vivo* after gene transfer of the desired gene into a subject in vivo for a gene therapy.

In view of the lack of guidance and data on whether any WAP promoter other than mouse mammary WAP promoter could direct gene expression in human mammary cells or in human mammary carcinoma cells, on whether a MMTV promoter can direct gene expression in any human cell type other than human mammary gland cells or human bladder carcinoma cells, and the unpredictable nature of a WAP promoter or a MMTV promoter in directing gene expression in different cell types, and the unpredictable nature of a WAP promoter or a MMTV promoter in directiing gene expression *in vivo*, it would have required a skilled person in the art at the time of the invention undue experimentation to have practiced over the full scope of the invention claimed. This is particularly true given the nature of the invention, the state of the prior art, the breadth of the claims, the amount of experimentation necessary, the absence of working examples and scarcity of guidance in the specification, and the unpredictable nature of the art.

The quantity of experimentation required to practice the claimed invention would include: isolation of putative WAP promoters and downstream genes, identification and characterization of WAP promoters derived from various organisms, determination of the WAP promoter function in its native cells, trial and error experimentation to determine the WAP promoter or MMTV promoter activity in directing gene expression in various cell types and cells derived from different organisms, and trial and error determination of the WAP promoter or MMTV promoter activity in directing gene expression in different cell types *in vivo*.

Applicants argue that Chen reference teaches β–gal could be of therapeutic relevance after viral delivery and one skilled in the art would not require undue experimentation to practice the claimed invention according to the teaching of the specification of the present application. Applicants further argue that Orkin does not discuss applicants' claimed invention and the teaching in Orkin reference is sufficient to establish that one skilled in the art would reasonably expect to use the known vectors. This is not found persuasive because of the following reasons:

Firstly, Chen reference teaches isolating splenocytes from BALB/c mice immunized with recombinant adenovirus expressing β-gal and adoptive transfer of said splenocytes produces dramatic regression of pulmonary metastases. Chen does not teach introducing any vector expressing β-gal via any administration route to a subject and exhibits therapeutic effects for a particular disease or disorder. Introducing any vector expressing β-gal via any administration route to a subject is different from introducing effector cells, i.e. splenocytes isolated from immunized mice to a subject. Further, Chen only suggests the use of recombinant adenovirus for the treatment of human cancers but does not specifically conclude or suggest the role of β-gal in the treatment of any cancer.

Secondly, the claims of the present application encompass any DNA construct in addition to the retroviral vector and Orkin points out the various problems encountered in using different vectors for gene therapy. Further, the art in gene therapy was unpredictable at the time of the invention and the disclosure of the present application is not sufficient and would require one

skilled in the art at the time of the invention undue experimentation to practice the claimed invention.

Applicants argue that Aebischer is a proponent of the encapsulation process for methods of treatment and that "the Patent Office cannot use later art-related facts that did not exist as of the filing date to test an application for compliance with the requirement of 35 U.S.C.112". This is not found persuasive because Aebischer may be a proponent of the encapsulation process but Aebiacher also points out various problems in using encapsulated cells for treatment of a disease or disorder and a proponent of the encapsulation process does not necessarily mean that any and all methods of using encapsulated cells for treatment of a disease or disorder would be successful and predictable. Further, Aebischer reference was published in 1991 which is before the priority date, 9-5-95, of the present application, and Orkin reference was published in December 1995 and is a review paper which references literatures well before December 1995.

Applicants argue that β-gal gene can be of therapeutic relevance after viral vector delivery (Chen reference) and one skilled in the art at the time of the invention would know that a WAP or a MMTV promoter could direct gene expression in any human cell type other than normal human mammary gland cells. This is not found persuasive because of the reasons set forth above and that the specification indicates "it is therefore not predictable that this regulatory element (WAP promoter) will function at all to direct expression in human mammary cells and/or allow expression in human mammary carcinoma cells" (page 2, lines 22-25) and also suggests that it is not obvious for one of ordinary skill that MMTV promoter or WAP promoter

would direct gene expression in human mammary cells. Although applicants later discover the MMTV promoter or the WAP promoter could direct gene expression in the human cells, this does not change the fact that it is unpredictable whether a MMTV promoter or a WAP promoter could direct gene expression in any human cell types other than the cell types disclosed, or direct gene expression in any cells other than human cells.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

7. Claims 1, 2, 9, 12-14, 16, 17, 26, 27, 36 are rejected under 35 U.S.C. 102(a) as being clearly anticipated by Gunzburg et al., WO 96/07748 (IDS-AQ).

The claims are directed to a retroviral vector comprising a heterologous gene or a therapeutic gene under the control of a MMTV promoter and said heterologous gene or therapeutic gene is expressed in a cell, such as a human cell, a method of expressing said heterologous gene in a human cell, a recombinant retroviral particle or provirus comprising said retroviral vector or a DNA construct containing a heterologous gene or a therapeutic gene under the control of a MMTV promoter, a packaging cell line harboring said retroviral vector, and an isolated human cell comprising said retroviral vector

Gunzburg teaches construction of a retroviral vector undergoing MMTV promoter conversion comprising a 5' LTR of the structure U3-R-U5, one or more coding sequence , and a 3' LTR region comprising a completely or partially deleted U3 region wherein said deleted U3 region is replaced by a polylinker sequence, followed by the R and U5 region, and the use of said retroviral vector for gene transfer vehicle for targeted gene therapy (e.g. abstract, p. 6). Gunzburg also teaches a retroviral provirus produced by replicating the retroviral vector in a retroviral vector system, a packaging cell line harboring retroviral constructs coding for the retroviral proteins which are not encoded in the retroviral vector set forth above, and said packaging cell line transfected with said retroviral vector (e.g. p. 7, 8, 24, 25). Gunzburg further teaches a therapeutic or non-therapeutic method for introducing homologous or heterololgous sequences into human or animal cells in vitro and in vivo by transfecting a packaging cell line of a retroviral system with the retroviral vector set forth above and infecting the targeted cells with the retrovirus produced by the packaging cell line (e.g. p. 23).

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 1, 2, 4, 5, 9-14, 16-19, 23-33, 36, 74-81, 91 and 92 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dranoff et al., 1993 (U2) in view of Lefebvre et al., 1991 (V2), Wilson et al., 1995 (X3), Archer et al., 1994 (U4), Gunzburg et al., WO 96/07748 (IDS-AQ) and Shao et al., 1994 (X2).

The claims are directed to a retroviral vector comprising a heterologous gene or a therapeutic gene under the control of a MMTV promoter and said heterologous gene or therapeutic gene is expressed in a cell, such as a human cell, a method of expressing said heterologous gene in a human cell, a recombinant retroviral particle or provirus comprising said retroviral vector or a DNA construct containing a heterologous gene or a therapeutic gene under the control of a MMTV promoter, a packaging cell line harboring said retroviral vector, and an isolated human cell comprising said retroviral vector, and a capsule encapsulating said packaging cell line.

Dranoff teach subcloning DNA sequences encoding the cytokine such as IL-4, IL-6, γ-IFN, a granulocyte-macrophage colony stimulating factor (GM-CSF), and adhesion molecules into retroviral vector MFG which contains Moloney murine leukemia virus (Mo-MuLV) long terminal repeat (LTR) and the resulting construct are introduced into CRIP packaging cells to generate recombinant virus which are used to transfect B16 melanoma cells. The transduced B16 cells are inoculated subcutaneously into C57BL/6 mice to monitor the delay of tumor formation associated with the synthesis of cytokine transgene (see e.g. abstract; result, first and second columns). Dranoff et al. does not teach using MMTV promoter for the expression of a gene in a

retroviral vector in human cells, and a capsule encapsulating the packaging cell line and said capsule comprising a porous capsule wall surrounding said packaging cell line.

Lefebvre reveals the presence of MMTV promoter and the positive and negative regulatory regions upstreams of MMTV promoter (see e.g. abstract) and indicates the hormone responsive element (HRE) (-70-0220) has been well characterized (e.g. introduction). Lefebvre et al. identifies an upstream element, located at the 5' end of the long terminal repeat (LTR), whose enhancer activity is restricted to mammary cells.

Wilson teaches transfection of human corneal endothelial cells with pMTV-D305 plasmid vector containing SV40 large T antigen (LTAg) under the control of mouse mammary tumor virus (MMTV) promoter and shows that SV40 LTAg mRNA continued to synthesized at significant levels in pMTV-D305-transfected cells in the absence of the inducer dexamethasone (e.g. p. 32, 33).

Archer teaches transfection of the human mammary carcinoma-derived cell line T47D(A1-2) with plasmid expressing luciferase reporter gene under the control of MMTV promoter and shows the luciferase gene is highly inducible by either glucocorticoids or progestins (e.g. abstract).

Gunzburg teaches construction of a retroviral vector undergoing MMTV promoter conversion comprising a 5' LTR of the structure U3-R-U5, one or more coding sequence , and a 3' LTR region comprising a completely or partially deleted U3 region wherein said deleted U3 region is replaced by a polylinker sequence, followed by the R and U5 region, and the use of said

retroviral vector for gene transfer vehicle for targeted gene therapy (e.g. abstract, p. 6). Gunzburg also teaches a therapeutic or non-therapeutic method for introducing homologous or heterololgous sequences into human or animal cells in vitro and in vivo by transfecting a packaging cell line of a retroviral system with the retroviral vector set forth above and infecting the targeted cells with the retrovirus produced by the packaging cell line (e.g. p. 23).

Shao et al. teaches microcapsules composed of collagen and encapsulated B16-F10 cells transduced with retrovirus containing GM-CSF gene into said microcapsule, and monitor the secretion of GM-CSF in the culture medium (e.g. experimental).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to substitute the Mo-MuLV LTR with MMTV promoter and use with any desired gene for the construction of a recombinant retroviral vector, a recombinant retrovirus containing said retroviral vector, or packaging cells harboring said retroviral vector, and a capsule encapsulating said packaging cells for the expression of any desired gene product in human mammary cells *in vitro or in vivo,* because Mo-MuLV LTR and MMTV promoter both are regulatory sequences derived from LTR and they both have function of directing gene expression and both Wilson and Archer teach gene expression under the control of MMTV promoter in human mammary carcinoma cells and human corneal endothelial cells.

One having ordinary skill in the art at the time the invention was made would have been motivated to do so in order to produce a retroviral vector comprising a heterologous gene or a therapeutic gene under the control of a MMTV regulatory sequence, a recombinant retroviral

particle produced by culturing a packaging cell line harboring said retroviral vector, a retroviral provirus carrying a construct comprising a heterologous gene or a therapeutic gene under the control of a MMTV regulatory sequence, a packaging cell line harboring said retroviral vector as taught by Dranoff et al., and a capsule encapsulating the packaging cells as taught by Shao et al. for generating a potent, specific and long lasting anti-mammary tumor immunity as taught by Dranoff and Lefebvre or to study the modulation of the chromatin environment by steroid receptors in defining their capacity to regulate gene expression and the mechanisms that regulates the proliferation of the human corneal endothelial cells as taught by Archer and Wilson.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (703) 305-1678. The examiner can normally be reached on Monday to Friday from 9 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Clark can be reached on (703) 305-4051. The fax phone number for this group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

Shin-Lin Chen, Ph.D.

Karen M. Hauda

KAREN M. HAUDA
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600